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Enteroviral Meningitis Does Not Exclude Concurrent Bacterial Meningitis

We read with interest the study of Nolte et al. (6) evaluating a completely automated enteroviral real-time PCR assay (EV-PCR) with cerebrospinal fluid (CSF). Among 434 patients, 113 (26%) had enteroviral meningitis with no bacterial coinfection. Six patients had bacterial meningitis with EV-PCR-negative CSF. In accordance with the work of Nigrovic et al. (5), who found no bacterial coinfection among 735 patients with enteroviral meningitis, they conclude that EV-PCR-positive CSF may lead to rapid patient discharge without antibiotic treatment.

However, we wish to describe two recent cases, diagnosed in 2010 at Robert-Debré Hospital, Paris, France, which illustrate the fact that EV-PCR positivity does not rule out the possibility of bacterial coinfection.

The first case involved a previously healthy 5-year-old boy. On admission, he had a temperature of 36°C, with headache and nuchal rigidity. One week previously, he had received a 5-day course of amoxicillin (80 mg/kg of body weight/day) for fever and headache. The leukocyte count was normal, the C-reactive protein level was <10 mg/liter, and procalcitonin was at <0.1 ng/ml. CSF analysis showed 638 cells/mm^3 (89% lymphocytes), 0.37 g/liter protein, and 4.2 mmol/liter glucose. Gram staining was negative. EV-PCR using the GeneXpert enterovirus assay (Cepheid, Maurens-Scopont, France) was positive. However, *Streptococcus pneumoniae* soluble antigens were detected (Binax Now), and *S. pneumoniae* PCR with CSF was positive (3). Blood and CSF cultures were negative. He was discharged after a 10-day course of cefotaxime (200 mg/kg/day) and vancomycin (60 mg/kg/day).

In the second case, a 14-year-old boy with renal graft-versus-host disease was admitted to the nephrology unit with a typical meningeal syndrome, including fever (38.3°C) and very high blood pressure. A ceftriaxone bolus (50 mg/kg) was immediately administered. Computed tomography (CT) scan was normal. The leukocyte count was 11,300/mm^3, the C-reactive protein level was 20 mg/liter, and the procalcitonin level was 0.9 ng/ml. CSF analysis showed 710 cells/mm^3 (91% neutrophils), 0.25 g/liter protein, and 3.7 mmol/liter glucose. Gram staining and culture of the CSF were negative. CSF was positive by both EV-PCR and *Neisseria meningitidis* serogroup B PCR (8). He was discharged after a 7-day course of cefotaxime (200 mg/kg/day).

In 1996, Dronkert et al. (4) noted that since the first description of concomitant viral and bacterial meningitis (9), only 14 cases had been published. However, Sferra et al. found that CSF samples from up to 2.8% of their 276 patients were positive by both viral and bacterial culture (7). Since 2007, in our hospital, 2 (1.3%) of 150 patients with EV-PCR-positive CSF were also positive for bacteria. Although representing a major advance, the completely automated PCR systems like the GeneXpert automat may paradoxically constitute a risk in the rare cases of bacterial coinfection, especially considering that up to 30 to 50% of children may have received antibiotics before CSF sampling (1, 2). Although rare, failure to diagnose mixed meningitis and thus to prescribe timely antibacterial chemotherapy may have dramatic consequences. Rapid sensitive techniques should be systematically used to search for at least *S. pneumoniae* and *N. meningitis* in CSF with pleocytosis, especially in antibiotic-pretreated children in industrialized countries.

REFERENCES

1. **Bryant, P. A., et al.** 2004. Prospective study of a real-time PCR that is highly sensitive, specific, and clinically useful for diagnosis of meningococcal disease in children. J. Clin. Microbiol. **42:**2919–2925.
2. **Chiba, N., et al.** 2009. Rapid detection of eight causative pathogens for the diagnosis of bacterial meningitis by real-time PCR. J. Infect. Chemother. **15:**92–98.
3. **Dagan, R., et al.** 1998. Prospective study to determine clinical relevance of detection of pneumococcal DNA in sera of children by PCR. J. Clin. Microbiol. **36:**669–673.
4. **Dronkert, M. L., A. G. Ketel, and R. de Groot.** 1996. Simultaneous occurrence of group B *Streptococcus* and *echovirus* 20. Eur. J. Pediatr. **155:**915.
5. **Nigrovic, L. E., R. Malley, D. Agrawal, and N. Kuppermann.** 1221. Low risk of bacterial meningitis in children with a positive enteroviral PCR test result. Clin. Infect. Dis. **51:**1221–1222.
6. **Nolte, F. S., et al.** 2011. Evaluation of a rapid and completely automated real-time reverse transcriptase PCR assay for diagnosis of enteroviral meningitis. J. Clin. Microbiol. **49:**528–533.
7. **Sferra, T. J., and D. L. Pacini.** 1988. Simultaneous recovery of bacterial and viral pathogens from cerebrospinal fluid. Pediatr. Infect. Dis. J. **7:**552–556.
8. **Taha, M. K.** 2000. Simultaneous approach for nonculture PCR-based identification and serogroup prediction of *Neisseria meningitidis*. J. Clin. Microbiol. **38:**855–857.
9. **Wright, H. T., Jr., R. M. McAllister, and R. Ward.** 1962. "Mixed" meningitis. Report of a case with isolation of *Haemophilus influenzae* type B and ECHO virus type 9 from the cerebrospinal fluid. N. Engl. J. Med. **267:**142–144.

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Authors' Reply

We appreciate the letter by Basmaci and colleagues. However, we disagree with their assessment that the GeneXpert enterovirus (EV) reverse transcriptase PCR (RT-PCR) assay "paradoxically constitutes a risk in rare cases of bacterial coinfection."

The clinical evaluation of a patient, as well as the interpretation of any laboratory result, must be made in the context of all available historical, clinical, and laboratory information. In the rare occurrences of EV-bacterial cerebrospinal fluid (CSF) coinfection, the bacterium-related clinical, laboratory, or historical findings are usually sufficient to dissuade the physician from discontinuing antibiotics. In their report, Sferra and Pacini note that the cytochemical analyses of the CSF of all patients revealed findings "typical of bacterial meningitis" and that the EVs made no contribution to the clinical pictures of the cases (7). Our review of the remaining reported cases of confirmed EV-bacterium coinfection revealed that in all but one, historical, clinical, or laboratory findings were present that were suggestive of bacterial meningitis (1–5, 9).

Similarly, the cases presented by Basmaci et al. had historical, clinical, or laboratory findings that suggested a possible bacterial etiology and would have prompted additional rigor in excluding a bacterial etiology. In the first case, the child received antibiotics for treatment of fever and headache, findings consistent with meningitis, 1 week earlier, thus raising the possibility of partially treated bacterial meningitis. The appropriate evaluation of this child would include a thorough search for a bacterial etiology using all tests available, as was done. In the second case, by virtue of graft-versus-host disease, the patient would have been considered to be immunocompromised and therefore at greater risk for bacterial infections. The finding of a predominantly polymorphonuclear (PMN) leukocyte pleocytosis in the CSF further suggested the possibility of a bacterial infection. In both of Basmaci's cases, it is most likely that prudent physicians would undertake thorough efforts to exclude a bacterial etiology.

In addition to the above, the dramatic change in the incidence and etiology of bacterial meningitis in children and adults over the last 30 years, due in large part to the introduction of conjugate vaccines against the common pediatric pathogens, would further reduce the likelihood of the occurrence of a silent bacterial coinfection in a case of EV meningitis (8). Following the introduction of *Haemophilus influenzae* type B (Hib) conjugate vaccine, the rate of bacterial meningitis in the United States has declined by 55%.

A recent surveillance report spanning 1998 to 2007 documented further reductions in the incidence of bacterial meningitis due to *Streptococcus pneumoniae* (1.09 versus 0.81 cases/100,000 population), *Neisseria meningitidis* (0.44 versus 0.19 cases/100,000 population), Hib (0.12 versus 0.8 cases/100,000 population), and *Listeria monocytogenes* (0.10 versus 0.05 cases/100,000 population). Reductions in the incidence of bacterial meningitis have occurred in all age groups with the exception of infants of <2 months of age, where *Streptococcus agalactiae* remains the major causative organism (8). Assuming the availability of conjugate vaccines for Hib and *S. pneumoniae* and appropriately timed immunization, up to 55% of cases of bacterial meningitis with coinfection with EV in children could have been prevented.

Based on the discussion above, we believe that a presentation of clinically silent bacterial central nervous system (CNS) infection superimposed on that of typical of EV meningitis would be extraordinarily unlikely (6). Of course, as with all other laboratory tests, interpretation of EV RT-PCR assays such as GeneXpert requires sound clinical judgment and must be made in the context of all available historical, clinical, and laboratory information.

REFERENCES

1. **Dickinson, R. J., J. M. Murdoch, and E. Edmond.** 1976. Simultaneous infection of the meninges by Coxsackie B virus and *Neisseria meningitidis* in an elderly female. Lancet **ii:**1412.
2. **Dronkert, M. L., A. G. Ketel, and R. de Groot.** 1996. Simultaneous occurrence of group B Streptococcus and echovirus 20. Eur. J. Pediatr. **155:**915.
3. **Elgin, R. P., et al.** 1984. Simultaneous bacterial and viral meningitis. Lancet **ii:**984.
4. **Hutchinson, D. N., A. G. Hesling, and W. M. Darling.** 1977. Simultaneous bacterial and viral infections of meninges. Lancet **i:**371.
5. **Nishmi, M., et al.** 1971. A winter outbreak of ECHO virus type 9 meningitis in Jerusalem, with cases of a simultaneous mixed pneumococcal-viral infection. Isr. J. Med. Sci. **7:**1240–1247.
6. **Romero, J. R., and H. A. Rotbart.** 2003. Enteroviruses, p. 1427–1438. *In* P. R. Murray et al. (ed.), Manual of clinical microbiology, 8th ed. American Society for Microbiology, Washington, DC.
7. **Sferra, T. J., and D. L. Pacini.** 1988. Simultaneous recovery of bacterial and viral pathogens from cerebrospinal fluid. Pediatr. Infect. Dis. J. **7:**552–556.
8. **Thigpen, M. C., et al.** 2011. Bacterial meningitis in the United States, 1998–2007. N. Engl. J. Med. **364:**2016–2025.
9. **Wright, H. T., A. R. McAllister, and R. Ward.** 1962. "Mixed" meningitis. Report of a case with isolation of *Haemophilus influenzae* type B and ECHO virus type 9 from the cerebrospinal fluid. N. Engl. J. Med. **267:**142–144.

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